REMARKS

Applicants thank the Examiner for the interview of 17 December 2004, and for the indication that, upon filing of a Request for Continued Examination, the focus of examination would be directed towards methods for treating neuronal deficiencies caused by neurodegenerative diseases (e.g., Parkinson's Disease) and vascular diseases (e.g., stroke). It is Applicants' belief that the redirection of prosecution is consistent with the art cited by the Examiner and the Applicants during the course of prosecution, as almost of the cited art is directed towards these two categories of diseases.

The withdrawn claims (22-34) are canceled merely to simplify prosecution. Applicants reserve the right to pursue similar claims in a divisional or other subsequent filing. Claim 1 is amended solely to expedite prosecution. Applicants reserve the right to pursue the unamended form of claim 1 in a subsequent application. The amendments to claim 1 are supported by the specification generally. Examples of support for particular terms may be found as follows: "vascular administration", see claim 14 as originally filed; "autologous, syngeneic or allogeneic", see page 25, paragraph 0055; "Parkinson's Disease", see page 18, paragraph 0038; "vascular disease", see page 22, paragraph 0047. New claim 35 is similarly supported. Claims 2, 3, 14 and 18-20 are canceled solely to conform the claim set to the amendments of claim 1, either by eliminating redundant subject matter or by eliminating subject matter that is no longer properly dependent from claim 1. Claims 15 and 16 are amended solely to maintain proper dependencies.

No new matter has been introduced.

II. THE PENDING CLAIMS COMPLY WITH 35 USC §112, 1ST PARAGRAPH

The Examiner maintains that claims 1-21 do not comply with the enablement requirement. The Examiner repeatedly notes that the alleged lack of enablement is related to the scope of the claims and to the lack of enablement for the treatment of congenital neurological disorders. For example, the Examiner writes, "Assuming the declaration [of Dr. Brazelton] will be perfected, the specification and the declaration still fails to support the full scope of the claimed invention because the claims encompass administration by any route." The Examiner

further writes, "Applicants submit post-filing evidence of Hess et al and Chen et al as support for enablement...However it is noted that both references study a brain ischemic model, not congenital neuron deficiency."

Applicants continue to maintain that the specification and post-filing date evidence are broadly enabling for reasons previously made of record and in view of the perfected Declaration of Dr. Timothy Brazelton.

Nonetheless, in order the expedite prosecution, the claims are amended so as to eliminate xenogeneic cell transplants and so as to focus on vascular delivery of cells for the treatment of neuronal deficiencies resulting from Parkinson's disease and vascular diseases. Applicants believe that the claims as amended are fully enabled.

The application as filed presents an actual reduction to practice of a method in mice, where bone marrow derived cells were administered intravascularly to mice and found to have engrafted into mouse brains and to have given rise to neuronal cell types. These data were published in the scientific literature and the findings have been confirmed or extended by many others. See, for example, Hess et al. (Stroke 2002 33:1362-8), Reference AT.

The Declaration of Dr. Brazelton describes experiments using the intravascular administration of bone marrow cells to alleviate Parkinsonian symptoms in a well-respected mouse model for Parkinson's disease. The information provided in the Declaration demonstrates that the methodology described in the present application at the time of filing can be practiced successfully to ameliorate the symptoms of a neurodegenerative disorder, such as Parkinson's disease.

Additionally, other scientists in the field have used methods described in the present application to achieve beneficial results in rodent models for stroke. Chen et al. (Reference AR, Chen J, Li Y, Wang L, Zhang Z, Lu D, Lu M, Chopp M. Stroke 2001 Apr;32(4):1005-11) administered bone marrow derived cells to rats having neurological damage resulting from induced events that closely resemble stroke in humans. Chen et al. administered cells intravenously and achieved significant improvement in recovery of neurological functions. While Chen et al. did not design their experiments to allow post-treatment identification of transplanted cells in the brain, Hess et al. (Reference AT; Hess DC, Hill WD, Martin-Studdard

A, Carroll J, Brailer J, Carothers J. Stroke 2002 May;33(5):1362-8) used histological methods to confirm that bone marrow derived cells administered to an animal model for stroke contribute to the neuronal cell population in the affected brains. Vascular diseases, such as stroke, tend to affect neuronal cells through a similar mechanism (generally a hypoxic effect coupled with an inflammatory effect), and thus it is reasonable to conclude that treatments which show in vivo effectiveness for stroke will also show in vivo effectiveness for other vascular disorders that damage neuronal cells.

Taken together, the data presented in the Declaration, and the data of Chen et al., and Hess et al. demonstrate that bone marrow derived cells can in fact be administered to a mammal suffering from a neuronal deficiency caused by Parkinson's disease or a vascular disorder, as taught by the specification, so as to ameliorate one or more symptoms.

Applicants respectfully request reconsideration and withdrawal of the rejections of the pending claims for alleged lack of enablement.

II. THE CLAIMED SUBJECT MATTER IS NOT ANTICIPATED OR RENDERED OBVIOUS BY THE ART

U.S. Patent Publication No. 2002/0146821 to Sanchez-Ramos et al. (the '821 publication)

The Examiner has rejected claims 1-10 and 13-21 as anticipated by the '821 publication under 35 U.S.C. § 102(e). The Examiner has also rejected claims 1, 8, and 10-12 as unpatentable over the '821 publication in view of Weiss et al. U.S. Patent No. 6,071,889.

Applicants note that Sanchez-Ramos do not teach vascular administration of bone marrow derived cells. In fact, the only methods taught by Sanchez-Ramos involve extensive culturing of bone marrow derived cells in vitro until the cells assume a neuronal phenotype, followed by administration of the cells directly to the CNS. It may be that the cultured cells of Sanchez-Ramos would not successfully travel through the blood stream to the CNS. Accordingly, Sanchez-Ramos does not teach all the limitations of the pending claims and therefore can not anticipate the claims.

Applicants wish to draw the Examiner's attention to a publication by the inventors listed on the '821 publication. In this publication, Sanchez-Ramos et al. (Reference AU) disclaim the very same in vivo data that is presented in example 3 of the '821 publication. Sanchez-Ramos et al. explain that beta-galactosidase is an unreliable and difficult marker to use in neurological cell transplant experiments. Neuronal cells tend to express high levels of endogenous beta-galactosidase, meaning that it is difficult to differentiate transplanted and endogenous cell types. Beginning at page 658, Sanchez-Ramos describe the beta-galactosidase approach as a "booby trap", and they describe in detail the very experiments and data that are presented in example 3 of the '821 publication. At page 660, Sanchez-Ramos et al. write, "At first blush, these results suggested the astounding result that *lacZ*-expressing, donor-derived, BMSC's had migrated extensively and had differentiated into neural cells in a site-dependent manner. However...we were observing factitious X-gal staining that was leading to the misidentification of endogenous cells as donor-derived cells."

Therefore, the inventors of the '821 publication have themselves rejected their own data showing the in vivo capability of bone marrow derived cells to become neurons. Sanchez-Ramos et al. also refer to the discovery presented in the instant application as a result that would be "astounding". Accordingly, one of ordinary skill in the art would not read the '821 publication and the accompanying Sanchez-Ramos reference as suggesting that bone marrow derived cells can, in vivo, maintain neuronal fates that would be useful in treating a neurological disorder.

Based on this evidence, Applicants assert that one of ordinary skill would not have been motivated to combine the teachings of Sanchez-Ramos with any other teaching, and that the disclaimed portions of Sanchez-Ramos are wholly unsupportive of any obviousness rejection.

While Applicants believe it to be unnecessary at this time, Applicants reserve the right to file a Declaration pursuant to 37 CFR 1.131 to demonstrate invention prior to the earliest valid priority date of the '821 publication.

Applicants respectfully request reconsideration of all rejections under 35 U.S.C. § 102(e) and 103(a) in view of the '821 publication.

REMARKS

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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